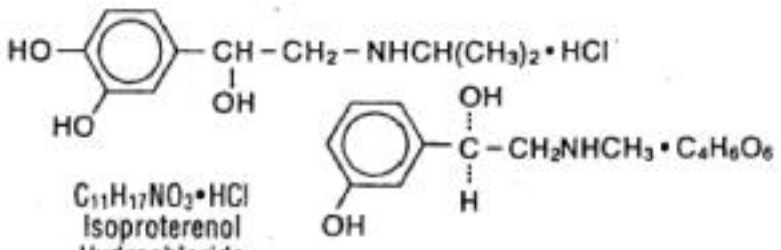
DUO-MEDIHALER - isoproterenol hydrochloride and phenylephrine bitartrate aerosol, metered
3M Pharmaceuticals

Inhalation Aerosol
PHARMACIST: Tear off 'Patient Instructions for Use" and dispense with product.

DESCRIPTION

DUO-MEDIHALER (isoproterenol hydrochloride and phenylephrine bitartrate) is a combination of two sympathomimetics administered by oral inhalation for the treatment of bronchoconstriction. Each metered dose of the aerosol delivers through the oral adapter 0.16 mg isoproterenol hydrochloride and 0.24 mg phenylephrine bitartrate of appropriate particle size (the majority less than 5 μ). This drug product also cortains cetylpyridinium chloride, dichlorodifluoromethane, dichlorotetrafluoroethane, sorbitan trioleate, and trichloromonofluoromethane. Chemically, isoproterenol hydrochloride is 4-[1-hydroxy-2-[(1-methytethyl)amino]ethyl]-1,2-benzenediol hydrochloride and phenylephrine bitartrate is (-)-*m*-hydroxy--*a*-[(methylamino) methyl]benzyl alcohol bitartrate.
Structural formulae:



$C_{11}H_{17}NO_3 \cdot HCl$
Isoproterenol
Hydrochloride
Molecular Wt. 247.72

$C_9H_{13}NO_2 \cdot C_4H_6O_6$
Phenylephrine Bitartrate
Molecular Weight 317.30

CLINICAL PHARMACOLOGY

Isoproterenol acts directly on beta-adrenergic receptors and phenylephrine acts directly on alpha-adrenergic receptors. The beta-adrenergic effects stem from the release of cyclic AMP following activation of the enzyme adenyl cyclase. Alpha-adrenergic effects probably result from inhibition of adenyl cyclase. Isoproterenol produces bronchodilatation, systemic vasodilation, mild hypotension, and tachycardia. Phenylephrine produces mild bronchodilatation, systemic vasoconstriction, mild hypertension, and bradycardia. These two drugs appear to act synergistically to allow the expression of each product's ability to relax bronchial smooth muscle. The vasoconstrictor effect of phenylephrine reduces bronchiolar blood flow thereby producing a decongestant effect, promotes retention of the drug in the bronchial mucosa, and blocks the tachycardia of isoproterenol. After oral inhalation of the combination, the pulmonary effects occur within a few minutes and persist up to three hours.
Studies demonstrate that the ventilatory effects of isoproterenolphenylephrine are superior to those obtained with the administration of isoproterenol alone. Because isoproterenol is a potent vasodilator that lowers blood pressure and acts upon the heart to increase cardiac output and pulse rate, its combination with phenylephrine results in a product with fewer cardiovascular effects. Studies have shown the absence of tachycardia and hypotension.
Isoproterenol alone often lowers arterial blood oxygen (PO_2). Several studies have shown that the combination of isoproterenol and phenylephrine rarely produces a significant drop in arterial oxygen tension while usually producing an increase in P_aO_2 in asthmatic patients.
Pharmacokinetics: The average half-life for isoproterenol administered by aerosol was five minutes. A plasma concentration of 0.03 ng/ml was found within minutes following an inhalation dose of 500 mcg isoproterenol.
Isoproterenol excretion following oral or inhalation administration is primarily renal. When given by inhalation, the major metabolite is the sulfate conjugate of the drug. When the drug is administered directly into the bronchial tree, it is inactivated by the enzyme catechol-*o*-methyl transferase, and the predominant metabolite is 3-*o*-methylisoproterenol sulfate. The explanation for this difference is supported by the observation that most (90%) of an aerosol dose is deposited in the mouth, swallowed, and converted to its sulfate conjugate in the gut wall, and to a lesser extent in the liver. The remaining isoproterenol is excreted as follows: 1% to 2% unchanged, 1% to 2% free methylated metabolite, and small amounts of metabolites in the bile.
Plasma levels following inhalation of phenylephrine have not been reported. Following oral and intravenous administrations, the average half-life was about 2.5 hours. Phenylephrine is metabolized in the liver and intestine by the enzyme monoamine oxidase. About 80% of a dose is recovered in the urine, primarily as phenolic conjugates and *m*-hydroxymandelic acid. About 16% of a dose is excreted as unchanged drug following intravenous administration and, due to first pass metabolism, less than 3% is excreted unchanged following oral dosing.
Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were concomitantly administered. The significance of these findings when applied to human usage is currently unknown.

INDICATIONS AND USAGE
DUO-MEDIHALER is indicated for the treatment of bronchospasm associated with acute and chronic asthma and reversible bronchospasm which may be associated with chronic bronchitis or emphysema.

CONTRAINDICATIONS
DUO-MEDIHALER must not be used by patients with known hypersensitivity to sympathomimetics. The use of isoproterenol in patients with pre-existing cardiac arrhythmias associated with tachycardia is contraindicated because the cardiac stimulant effects of the drug may aggravate such disorders.

WARNINGS
Excessive use of an adrenergic aerosol should be discouraged, as it may lose effectiveness. Occasional patients have been reported to develop severe paradoxical airway resistance with repeated, excessive use of isoproterenol inhalation preparations (see ADVERSE REACTIONS). The cause of this is unknown. It is advisable that in such instances the use of this preparation be discontinued immediately and alternative therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn. Deaths have been reported following excessive use of isoproterenol inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several instances (see ADVERSE REACTIONS).

PRECAUTIONS
General: As with all sympathomimetic drugs, DUO-MEDIHALER should be used with great caution in the presence of coronary insufficiency, hypertension, hyperthyroidism, and diabetes.
Information for Patients: Patients who are being treated with DUO--MEDIHALER should be informed adequately of the dangers of overusage, tolerance and rebound bronchospasm (see WARNINGS and ADVERSE REACTIONS sections). They should be instructed to take no more than two inhalations at any one time, nor more than six in any one hour during a 24-hour period, unless advised by the physician (see DOSAGE AND ADMINISTRATION and Patient Instructions for Use sections).
Isoproterenol may cause the patient's saliva to turn pinkish to red in color. Proper use of DUO-MEDIHALER oral inhaler should be demonstrated and discussed. Patient Instructions for Use are available with the package insert and should be provided when the medication is dispensed.
As with any drug, patients should be advised against the ingestion of alcohol during treatment.
Drug Interactions: A monoamine oxidase (MAO) inhibitor, a tricyclic antidepressant, or guanethidine may increase the cardiac and pressor effects of phenylephrine and isoproterenol; however, normal volunteers given isoproterenol by inhalation along with an MAO inhibitor or a tricyclic antidepressant had no adverse cardiovascular effects.
Arrhythmias may result from the concurrent administration of isoproterenol or phenylephrine to patients who are receiving digitalis, epinephrine, cyclopropane, or halogenated hydrocarbon anesthetics.
Beta-adrenergic blocking drugs such as propranolol antagonize the cardiac, bronchodilating, and vasodilating effects of isoproterenol and the stimulating effects of phenylephrine.

Ergot alkaloids may increase blood pressure in patients receiving isoproterenol or phenylephrine. Phentolamine mesylate (Regitine®), an alpha-adrenergic blocker, may decrease the pressor response to phenylephrine.
Phenothiazine drugs have some alpha-adrenergic blocking activity and may reduce the pressor effects and duration of action of phenylephrine.
Drug/Laboratory Test Interactions: Isoproterenol causes false elevations of bilirubin as measured *in vitro* by sequential multiple analyzer. An effect on serum bilirubin determinations in patients receiving the drug has not been determined. One case of surreptitious self-administration of a 500 mg subcutaneous dose of isoproterenol resulted in increased urinary excretion of epinephrine, norepinephrine, and vanilmandelic acid. Isoproterenol inhalation may result in enough absorption of the drug to produce increased values for urinary epinephrine. This effect is probably small with standard doses, but is likely to increase with larger doses.
Carcinogencity, Mutagenesis, and Impairment of Fertility: Isoproterenol hydrochloride, phenylephrine bitartrate, or DUO--MEDIHALER have not been evaluated for carcinogenicity, mutagenicity or impairment of fertility.
Pregnancy: Teratogenic Effects - Pregnancy Category C: Reproduction studies have not been done with DUO-MEDIHALER or phenylephrine. Reproduction studies with isoproterenol have been performed in rats and rabbits with aerosol doses (30 minutes per day for 12 days) up to 15 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. It is also not known whether DUO-MEDIHALER can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DUO-MEDIHALER should be given to a pregnant woman only if clearly needed.
Labor and Delivery: DUO-MEDIHALER has no recognized use during labor and delivery. Phenylephrine administration during late pregnancy or labor may cause fetal anoxia and bradycardia by increasing uterine contractility and decreasing uterine blood flow.
Nursing Mothers: It is not known whether isoproterenol or phenylephrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DUOMEDIHALER is administered to a nursing woman.
Pediatric Use: Safe and effective use of DUO-MEDIHALER in children below the age of 12 has not been established.
Geriatric Use: Lower doses in elderly patients may be required due to increased sympathomimetic sensitivity (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The following adverse effects, listed by organ system in decreasing frequency have been associated with the use of DUO-MEDIHALER and are similar to those produced by other sympathomimetic agents:

	Isoproterenol	Phenylephrine
Cardio-vascular:	palpitation	bradycardia
	tachycardia	decreased cardiac output
	coronary insufficiency	blanching of skin
	flushing of skin	peripheral and visceral vaso-constriction
	blood pressure changes	cardiac irregularities
	cardiac arrhythmias	anginal pain
	cardiac arrest	
	anginal pain	
	Isoproterenol	Phenylephrine
Pulmonary:	paradoxical airway resistance	respiratory distress
	rebound broncho-spasm	
Central Nerv-ous System:	headache	tremor
	tremor	dizziness
	vertigo	central excitation
	central excitation	pilomotor response
	insomnia	
Gastro-Intestinal:	nausea	

DRUG ABUSE AND DEPENDENCE

Drug abuse and dependence have not been reported with DUO--MEDIHALER.

OVERDOSAGE

Isoproterenol: The oral LD_{50} values are as follows: mouse, 1260 mg/kg; rabbit, 3070 mg/kg; male rat, 2230 mg/kg; female rat, 2840 mg/kg; and dog, 600 mg/kg. The intravenous LD_{50} values are as follows: mouse, 126 mg/kg; rabbit, 27 mg/kg; male rat, 96 mg/kg; female rat, 112 mg/kg; and dog, 50 mg/kg.

Phenylephrine: The oral LD_{50} values are as follows: rat, 350 mg/kg; and mouse, 120 mg/kg. The intravenous LD_{50} values are as follows: rat, 6.8 mg/kg; and mouse, 21 mg/kg.

Symptoms: The individual patient's sensitivity to either drug will dictate the overdosage signs. There is reason to believe, however, that the overdosage effects of either drug are antagonized by the other drug in the combination. Severe symptoms of overdosage are more likely to result from parenteral administration of isoproterenol rather than from oral inhalation of isoproterenol and phenylephrine in an aerosol.

Manifestations of acute overdosage include chest pain, dizziness, headache, irregular heartbeat, fast or pounding heartbeat, bradycardia, nausea or vomiting, restlessness, weakness, flushing, decreased diastolic pressure, convulsions, cerebral hemorrhage, or hypertension.

Treatment: Discontinued dosing allows rapid reversal of adverse effects. Blood pressure and ECG may be monitored and the following treatment used, as appropriate: Tachycardia in asthmatic patients may be treated with cardioselective beta-blockers (metoprolol or atenolol, but use cautiously since cardioselectivity may not be absolute) and in nonasthmatics with propranolol; bradycardia may be treated with atropine; blood pressure may be regulated with rapid-acting vasodilators (nitrites, sodium nitroprusside) or alpha-blocking agents (quinidine, phentolamine). It is not known if isoproterenol or phenylephrine are dialyzable.

DOSAGE AND ADMINISTRATION

Adults: The usual dose for the relief of dyspnea caused by acute bronchospasm is one or two inhalations. Start with a single inhalation. If no relief is evident after two to five minutes, a second inhalation may be taken. For daily maintenance, use one or two inhalations four to six times daily or as directed by the physician. The physician should be careful to instruct the patient in the proper technique of administration so that the number of inhalations per treatment and the frequency of retreatment may be titrated to the patient's response.

No more than two inhalations should be taken at any one time, nor more than six inhalations in any one hour during a 24-hour period, unless advised by the physician. Lower doses in elderly patients may be required due to increased sympathomimetic sensitivity. Each depression of the valve delivers through the oral adapter 0.16 mg isoproterenol hydrochloride and 0.24 mg phenylephrine bitartrate.
Children: Safety and effectiveness for children under 12 years have not yet been established (see Pediatric Use).

DIRECTIONS FOR USE

Before each use, remove dust cap and inspect mouthpiece for foreign objects. Shake DUO-MEDIHALER.

1. Breathe out fully and place mouthpiece well into the mouth aimed at the back of the throat.

2. As you begin to breathe in deeply, press the vial firmly down into the adapter with the index finger. This releases one dose.

3. Release pressure on vial and remove unit from mouth. Hold your breath as long as possible, then breathe out slowly.

Replace dust cap after each use.

HOW SUPPLIED

DUO-MEDIHALER is an aerosol device which delivers 0.16 mg of isoproterenol hydrochloride and 0.24 mg of phenylephrine bitartrate through the oral adapter with each depression of the valve.
15-ml vial and oral adapter, containing 21.0 gm, a minimum of 300 actuations
NDC **0089-0735-21**).
15-ml refill vial only, containing 21.0 gm, a minimum of 300 actuations (NDC **0089-0735-11**).
Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's).
WARNING: Contains trichloromonofluoromethane, dichlorodifluoromethane, and dichlorotetrafluoroethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.
A notice similar to the above WARNING has been placed in the "Patient Instructions for Use" of this product pursuant to EPA regulations.

CAUTION

Federal law prohibits dispensing without prescription. **CONTENTS UNDER PRESSURE.** Do not puncture or incinerate container
Store at controlled room temperature between 15°C and 30°C. (59°F and 86°F). **KEEP OUT OF THE REACH OF CHILDREN.**
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Northridge, CA 91324
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